REMARKS

The claims are not amended with this paper. Applicants note with appreciation that the prior rejections under 35 U.S.C. 102 have been withdrawn, and now request further reconsideration of the application in view of the amendments and remarks herein.

Interview Summary

Applicants thank the Examiner for the courtesy of permitting a telephonic interview on March 4, 2009 ("the Interview"). During the Interview, the rejections of record were discussed. Although the possibility of filing a Declaration was discussed, no final agreement was reached.

Rejection under 35 U.S.C. §112, first paragraph (enablement)

Claims 4 and 11 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. This rejection is traversed.

Claim 4 (as now pending), from which claim 11 depends, is directed to a method of evaluating onset or onset possibility of rheumatoid arthritis in a human subject, the method comprising the steps of detecting whether a gene coding a protein comprising the amino acid sequence of SEQ. ID NO.:1 is present homozygously in the subject; and evaluating the onset or onset possibility of rheumatoid arthritis in the subject; wherein the homozygous presence of the gene in the subject is indicative of an increased possibility of onset of rheumatoid arthritis in the subject.

The Office Action discusses the Wands factors and states that claims 4 and 11 lack enablement. Applicants do not agree.

As previously noted, the pending claims are directed to a method in which, *inter alia*, the homozygous presence of the gene in the subject is indicative of an increased possibility of onset of rheumatoid arthritis in the subject.

Further, as discussed previously, the present application and the "Declaration Under 37 CFR 1.132" (the "August 2007 Declaration") filed September 11, 2007, each

provide evidence showing that there is a statistical trend showing that presence of a gene coding a protein comprising the amino acid sequence of SEQ. ID NO.:1 homozygously in the subject, is associated with development of RA in a subject.

As described in the accompanying "Declaration Under 37 CFR 1.132" of Shunichi Shiozawa dated April 1, 2009 (the "April 2009 Declaration"), in one experiment, PCR was performed as described to obtain a partial sequence of Angiopoietin-1 from whole RNA of whole blood of RA patients and healthy subjects. The subjects were selected from the general population in Japan.

In this experiment, total RNA was extracted from 300μl of whole blood from RA patients or healthy subjects. By reverse transcription reaction using an Oligo dT primer carried out in the usual method known in the art, a first strand cDNA was synthesized. With the cDNA used as a template, amplification of a region including a mutated site was carried out by a two-step RT-PCR using the primers described. The second-step PCR was carried out by using, as a template, 1μl of product obtained by the first-step PCR. A PCR product obtained by the second-step PCR was subjected to a sequence analysis and an analysis on long chain in the usual method known in the art, so as to determine whether or not the 3-base-insertion/deletion occurred at positions No. 805 to No. 807 in an Angiopoietin-1 gene.

The results of the experiment are shown in the Table in the April 2009 Declaration, and indicate that the occurrence of the homozygous insertion mutation ("3bp insertion Homo") at position Nos. 805 to No. 807 in Ang-1 is associated with the occurrence of RA in the subjects studied (there is a significant difference, $p < 0.005$). Applicants note that there were 69 RA subjects who had the "3bp insertion Homo" genotype.

With respect to the data presented, according to the April 2009 Declaration, the data shown in the Table in Paragraph 5 of the April 2009 Declaration include results from the subjects included in the data provided in the Declaration dated August 27, 2007 (submitted with an amendment dated September 11, 2007). However, the analytical methods used in the two Declarations were different; the data provided in the August 2007 Declaration were obtained by analyzing the PCR products with an older,

less sensitive sequencing instrument, while the added data in the Table in the April 2009 Declaration were obtained using a higher performance sequencer. These differences in analysis may explain, at least in part, any differences in the data shown in the April 2009 Declaration as compared to the data provided in August 2007 Declaration.

In view of the data presented in the subject specification, and in the Declarations of August 2007 and April 2009, Applicants contend that one of ordinary skill in the art would be able to evaluate the onset or onset possibility of rheumatoid arthritis in a human subject by detecting the homozygous presence or absence of a gene coding a protein comprising the amino acid sequence shown in SEQ. ID NO.:1 (as described in the present application) in the subject, because the presence of the homozygous insertion mutation (the 3-base insertion at positions 805 to 807 in the nucleic acid sequence coding for Angiopoietin-1) is significantly associated with rheumatoid arthritis, e.g., as described in the experiment described herein.

Applicants further point out that the present claims are directed to a method of evaluating onset or onset possibility of rheumatoid arthritis in a human subject. Applicants contend that one of ordinary skill in the art would consider the presently-claimed method useful for evaluating onset or onset possibility of rheumatoid arthritis in a human subject, even if the correlation between the homozygous presence of the mutant gene and the development of RA is less than 100% (the statistical trend in the data of the most recent Declaration has been discussed above). In the April 2009 Declaration (as in the August 2007 Declaration), Dr. Shiozawa indicates that, in his view, it is possible to evaluate the onset or onset possibility of rheumatoid arthritis in a human subject by detecting the homozygous presence or absence of a gene coding a protein comprising the amino acid sequence shown in SEQ. ID NO.:1 (as described in the present application) in the subject, because the presence of the homozygous insertion mutation (the 3-base insertion at positions 805 to 807 in the nucleic acid sequence coding for Angiopoietin-1) is associated with rheumatoid arthritis. If desired, the present method could be used by a medical practitioner together with other diagnostic information to evaluate a subject's propensity for developing RA.

In view of the data presented in the subject specification, and in the Declarations, Applicants contend that one of ordinary skill in the art would be able to evaluate the onset or onset possibility of rheumatoid arthritis in a human subject by detecting whether a gene coding a protein comprising the amino acid sequence of SEQ. ID NO.:1 is present homozygously in the subject; and evaluating the onset or onset possibility of rheumatoid arthritis in the subject; wherein the homozygous presence of the gene in the subject is indicative of an increased possibility of onset of rheumatoid arthritis in the subject, as presently claimed.

The Office Action further discusses references (Hirschhorn et al. and Ioannides) that suggest that association studies are not reproducible. Applicants respectfully contend that no reason has been advanced to suggest that the studies presented in the present application and the Declarations are unreliable. To the contrary, as discussed herein, in addition to the data from the present application, an association between the homozygous presence of the mutant gene and the development of RA is seen in studies subsequent to the filing of the present application.

In the section titled "Response to Arguments", the Office Action states that the data provided in the specification and in the August 2007 Declaration do not provide "that the artisan could predictably determine the possibility of onset of RA at the art accepted level of a P value of 0.05 or less as described by Ioannidis." This statement is traversed. As noted above, the data provided with the April 2009 Declaration provides that the homozygous presence of the gene coding a protein comprising the amino acid sequence of SEQ. ID NO.:1 is significantly ($p < 0.005$) associated with RA. Thus, contrary to the statement in the Office Action, a statistical correlation has been observed. Applicants respectfully contend that any differences in gene or disease prevalence in the study populations do not call into question, and in fact confirm, that the pending claims are enabled.

Applicants respectfully contend that the specification provides enablement for the full scope of the pending claims, and, furthermore, that the claims meet all the requirements of, *inter alia*, 35 USC §112. Reconsideration and withdrawal of the rejection is requested.

CONCLUSION

For at least the above reasons, Applicants contend that the application is in condition for allowance. Early and favorable consideration of the application is earnestly solicited.

Applicants conditionally request any extension of time necessary for this response to be considered timely filed. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Reference No. 61646 (70904), Customer No. 21874.

Dated: April 6, 2009

Respectfully submitted,

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